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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/566,320	01/26/2006	Rhonan Ford	06275-490US1 101140-1P US	3505

26164 7590 06/04/2008

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EXAMINER
CHANDRAKUMAR, NIZAL S

ART UNIT	PAPER NUMBER
1625	

MAIL DATE	DELIVERY MODE
06/04/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/566,320	FORD ET AL.	
	Examiner	Art Unit	
	NIZAL S. CHANDRAKUMAR	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13,15 and 18-22* is/are pending in the application.

4a) Of the above claim(s) *13,15 and 18-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,11 and 12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *01/26/2008, 12/18/2006, 14/25/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

Applicants' response filed 04/25/2008 is acknowledged.

Status of the claim:

Following groups were presented in the Restriction Requirement filed 02/25/2008

Group 1-8, claim(s) 1-8, 11,12,14, drawn to compounds.

Group 2, claim(s) 9, drawn to process of making compounds.

Group 3, claim(s) 10, drawn to product in the process of Group 2.

Group 3, claim(s) 13, drawn to process of making pharmaceutical compositions.

Group 4, claim(s) 20,21, drawn to pharmaceutical method of use of compounds of Group I.

Claims 15-19 are not considered because the claims contain the non-statutory terminology "use of".

With correction as per the amended claims of 01/26/2006, the groups read as follows:

Claims 1-13, 15, 18-22 are pending. Claims 14, 16-17 are cancelled.

Group 1-8, claim(s) 1-8, 11,12 drawn to compounds.

Group 2, claim(s) 9, drawn to process of making compounds.

Group 3, claim(s) 10, drawn to product in the process of Group 2.

Group 4, claim(s) 13, drawn to process of making pharmaceutical compositions.

Group 5, claim(s) 15,18,19-22, drawn to pharmaceutical method of use of compounds of Group I.

Election/Restrictions

Applicant's election with traverse of Group 1, claims 1-8, 11,12 in the reply filed on 04/25/2008 is acknowledged. The traversal is on the ground(s) that the present application is a U.S. National Stage application. As such, the present application is subject to unity of invention practice in accordance with 37 CFR 1.475 and 1.499; and the Office must follow PCT Rule 13 and not national practice in these determinations. This is not found persuasive for reasons of record. Thus, the invariant structure, present in all the groups, i.e., quinoline ring system is well known in the art and as such is not a contribution over prior art (also see below, prior art cited for rejections under 35 USC § 102 and 35 USC § 103).

The requirement is still deemed proper and is therefore made FINAL.

Claims 9,10, 13, 15, 18-22, withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 04/25/2008.

This application contains claims 9,10, 13, 15, 18-22 drawn to an invention nonelected with traverse in the reply filed on 04/25/2008. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-8, claim(s) 1-8, 12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims are drawn to solvates without explicitly defining what chemical composition or structures of the compounds protection is sought for. Solvates (and hydrates) are defined in the art with chemical formulae such as (C8H6N2.HCl. 1.25 H2O).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-7, 12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a few quinoline compounds, does not reasonably provide enablement for the generic class of compounds claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and /or use the invention commensurate in scope with these claims. For example, enablement with respect to making aspect of the inventions is present for compounds of the formula p = 1, and R1 = Cl (at quinoline 6-positon) and q = 0. However the instant formulae encompass billions of quinoline compounds based upon about 80 R groups which are layered on top of each other, several repeat groups defined with many alphabets such as p ,q etc and unknown salts and solvates. Further, with respect to use aspect of the invention, the disclosure is limited to 4 examples, and the examples all having very close structural similarity. Thus the claims are extremely broad and the disclosure of the instant specification is not sufficient to support the generic formulae I.

The determination that “undue experimentation” would have been needed to make and use the

claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the relevant factual considerations.

Enablement is considered in view of the Wands factors (MPEP 2164.01 (a)).

The nature of the invention: The claims are drawn to quinoline compounds, and salts useful as P2X7 receptor antagonists.

The breadth of the claims: With the independently varying, approximately 80 variables layered with substituents on top of substituents, not to mention the stereo chemical possibilities, the number of theoretically conceivable compounds for the formulae is in billions rendering the scope of the claims large. Further, the formula encompasses molecules that widely vary in the physical and chemical properties such as size, molecular weight, logP, acidity and basicity, properties that are known in the art to greatly influence the PK and PD parameters, not to mention the ability to productively bind to claimed biological target molecules.

The level of the skill in the art: The level of skill in the art is high. However, due to the unpredictability in the art of drug discovery, it is noted that each embodiment of the invention is required to be individually assessed for viability.

The presence or absence of working examples and the amount of direction or guidance present: The specification contains direction for making compounds in which the C6 position of the quinoline ring is substituted by chloro group. All the compounds in the specification were ultimately derived from, 5-bromo-6-chloroquinoline or 5-nitro-6-chloro-quinoline. While making amides (X variable) needs no guidance, the preparation of substituted quinolines with the claimed variables would require undue experimentation, because the chemistry disclosed in the specification is not extendable to the claimed substituents. For example, chemistry needed for making a R4 bromo substituted compound of formula (I) would be incompatible with the disclosed (Pd insertion) chemistry. Any conceivable synthetic scheme to

introduce this R4 bromo substituent after the introduction of the X variable would require undue experimentation because of regiochemical issues. Likewise, guidance by prior art citation or working example for R1 substitution at the other possible positions of the benzene portion of the quinoline is not present in the specification. Likewise, guidance is absent for making compounds wherein in q is other than 0 (zero). Guidance by prior art citation or working example for other substitutions is not seen in the specification. Guidance in the form of citation for possible sources for the starting materials or literature citation for making the starting materials in lieu of working examples is also absent in the specification.

There are 31 examples present in the specification, but it is not seen where in the specification enabling disclosure with respect solvates is present.

The biological activity disclosed is for four compounds which are very similar in structure, that is no SAR is discernable.

It is not seen wherein the specification, enabling disclosure is present for making R2 other than phenyl.

The state and the predictability of the art: In the absence of prior art teaching, absence of citations (commercial or literature) for the procuring needed starting materials for the preparation of substitutions other than the ones mentioned above, one skilled in the art attempting to make compounds of the present inventions would be faced with undue research burden. Further with the unpredictable nature of the medicinal chemistry art, without a disclosed or an established pharmacaphore, it is unpredictable what embodiment of the billion possibilities claimed would have desired biological activity.

The quantity of experimentation needed: In the instant case, there is a substantial gap between the compounds demonstrated and the breadth of the claims. Consequently, a burdensome amount of research would be required by one of ordinary skill in the art to bridge this gap. The instant disclosure is broad and generic. It is not clear what specific embodiments would be required in order for one of ordinary skill in the art at the time the invention was made to practice the instant invention commensurate in scope with the claims.

Taken together the above factors into consideration, enablement for making the compounds provided in the specification is limited to quinoline compounds of the formula I with the following variables: p = 1, q = 0, R1 = Cl at C6 of quinoline. R2 = optionally substituted phenyl.

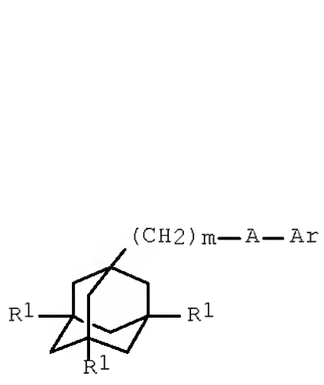
Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

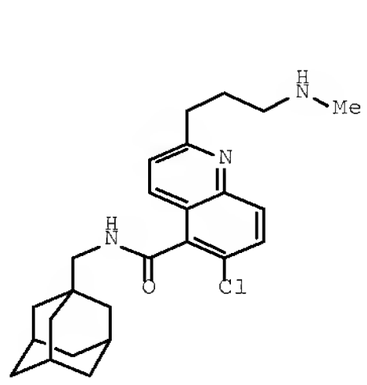
> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-8, 11,12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ford et al. (WO 03/080579 A1, International Filing Date 03.24.2003).

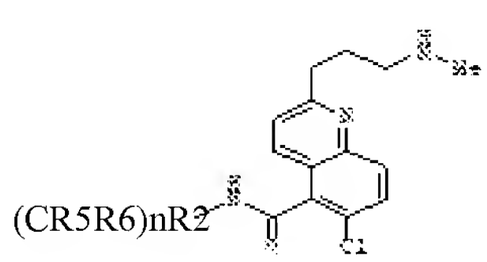
Ford et al. teach adamantyl quinolinylamides of general structure I including specific compounds such as II as P2X7 receptor antagonists



I



II



Instant case

The instantly claimed compounds are analogs of the compounds of Ford et al. in that the substituent (CH2)n-adamantyl of Ford et al is replaced with (CR5CR6)R2, in effect replacement of adamantyl group of Ford et al. compounds with R^2 4- to 10-membered unsaturated ring system (the enabling disclosure in the instant application for R2 is 6-memebered unsaturated ring system).

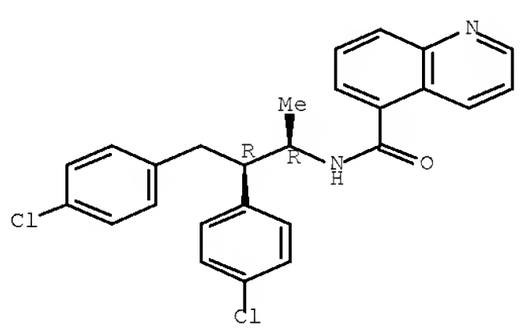
The instantly claimed lipophilic (CR5CR6)R2 is analogous to the lipophilic (CH2)n-adamantyl group. However the experienced Ph.D. medicinal chemist, would be motivated to prepare additional analogs of the prior art compounds, by replacing the adamantyl group with other cyclic groups with reasonable expectation of success because such structurally close analogs are anticipated to have similar properties and because of the routine nature of such analog design in the art of medicinal chemistry. The instantly claimed compounds would have been suggested and therefore, obvious to one skilled in the art. A strong case of *prima facie* obviousness has been established.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

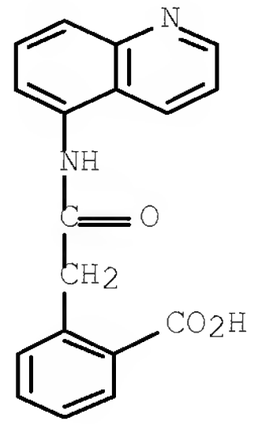
Claims 1-7, 11,12 rejected under 35 U.S.C. 102(e) as being anticipated by Hagmann et al. (WO 2003087037) which teaches



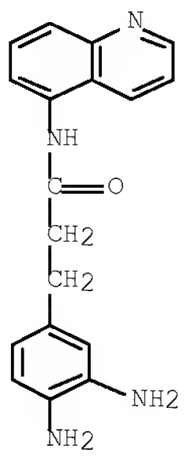
Corresponding to p = q = 0; R3 = R7 = H; n = 2, R5 = H, R6 = C1-alkyl, C5 = H, R6 = phenyl; R2 = unsaturated 6-memebered ring system.

Likewise,

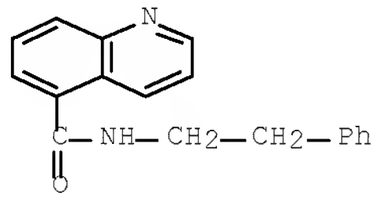
Claims 1-7, 11,12 rejected under 35 U.S.C. 102(b) as being anticipated by Modena et al. (Farmaco (1993), 48(4), 567-72) teach



Claims 1-7, 11,12 rejected under 35 U.S.C. 102(b) as being anticipated by Naruto et al (US 5643925) teach



Claims 1-7, 11,12 rejected under 35 U.S.C. 102(b) as being anticipated by Sharma et al. (Indian Journal of Chemistry, Section B: Organic Chemistry Including Medicinal Chemistry (1988), 27B(5), 494-7) teach



No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nizal S. Chandrakumar whose telephone number is 571-272-6202. The examiner can normally be reached on 8.30 am – 5 pm Monday- Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached at 571-272-0867 or Primary Examiner D. Margaret Seaman can be reached at 571-272-0694. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Nizal S. Chandrakumar

/D. Margaret Seaman/

Primary Examiner, Art Unit 1625